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ORIGINAL RESEARCH ARTICLE

Long-term clinical and haemodynamic results after transcatheter annuloplasty for secondary mitral regurgitation

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Abstract

Aims The study sought to investigate the long-term outcome after transcatheter mitral valve annuloplasty for secondary mitral regurgitation (MR).

Methods and results Consecutive patients with symptomatic secondary MR undergoing transcatheter mitral valve annuloplasty with the Carillon device at Leipzig University Hospital between 2012 and 2018 were studied prospectively. Left ventricular (LV) function and MR severity were quantified by standardized echocardiography. 33 patients were included. Mean age was 75 ± 10 years, and 20 patients were women. A Society of Thoracic Surgeons score of 8.1 ± 7.2% indicated high-risk status. In 24 patients, MR resulted from LV remodelling and dysfunction, eight suffered from left atrial dilatation, and one patient had MR due to combined primary and secondary aetiology. LV ejection fraction at baseline was (median) 38% [inter-quartile range (IQR) 30–49%]. During the mean follow-up time of 45 ± 20 months, 17 patients died, two patients withdraw consent, and four patients were lost. Of the remaining patients, four were hospitalized for decompensated heart failure. Two of these patients underwent additional transcatheter edge-to-edge mitral valve repair. At follow-up, New York Heart Association (NYHA) functional class improved from 95% in Class III/IV at baseline to 70% in Class I/II with no patients in NYHA Class IV ($P < 0.0001$). Mitral regurgitant volume was reduced from 27 mL (IQR 25–42 mL) to 8 mL (IQR 3–17 mL) ($P = 0.018$) and regurgitant fraction from 42% (IQR 34–54%) to 11% (IQR 8–24%) ($P = 0.014$). LV end-diastolic volume index [92 mL/m^2 (IQR 74–107 mL/m^2) vs. 67 mL/m^2 (IQR 46–101 mL/m^2), $P = 0.065$] and end-systolic volume index [50 mL/m^2 (IQR 44–69 mL/m^2) vs. 32 mL/m^2 (IQR 20–53 mL/m^2), $P = 0.037$] decreased. Total stroke volume remained unchanged [38 mL/m^2 (IQR 33–43 mL/m^2) vs. 33 mL/m^2 (IQR 26–44 mL/m^2), $P = 0.695$], while LV ejection fraction increased [43% (IQR 35–49%) vs. 54% (IQR 46–57%), $P = 0.014$]. Forward stroke volume, heart rate, and forward cardiac output were not significantly altered.

Conclusions Among high-risk patients undergoing transcatheter mitral valve annuloplasty for symptomatic secondary MR, mortality was ~50% at 4 years. In the surviving patients, reduced MR severity was associated with reduced NYHA functional class, reverse LV remodelling, and improved LV function.

Keywords Secondary mitral regurgitation; Mitral valve repair; Annuloplasty; Heart failure

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Introduction

Mitral regurgitation (MR) is the most common valvular heart disease.[1] While primary MR results from structural valve disease, secondary MR is caused by left ventricular (LV) dilatation and/or dysfunction, or left atrial (LA) dilatation.[1–3] Secondary MR contributes to morbidity and mortality and impairs survival in chronic heart failure.[4,5] Treatment of secondary MR is primary based on the underlying aetiology, that is, guideline-directed medical therapy for heart failure.[3,6] However, severe secondary MR imposes a volume load on the LV and the LA, which contributes itself to haemodynamic

deterioration, that is, congestion, heart failure symptoms, and cardiac decompensation.[1,7] This pathophysiological concept is the basis for structural interventions on the mitral valve for secondary MR to prevent the progression of heart failure.

A frequent mechanism of secondary MR is mitral annulus dilatation, caused by either LV or LA dilatation, precluding central leaflet coaptation. Mitral annulus dilatation can be treated with annuloplasty.[2,8] Prognostic data for surgical mitral annuloplasty are lacking.[6] Thus, a majority of the patients with severe secondary MR are not referred for mitral valve surgery, probably because most of them are high-risk patients due to the underlying heart failure and extracardiac co-morbidities.[9] Therefore, transcatheter techniques for mitral valve annuloplasty have been developed.[10]

The Carillon contour system is a transcatheter mitral valve annuloplasty (TMVA) fixed-length device with a double anchor, which is implanted in the coronary sinus surrounding the mitral annulus. Thereby, the annulus becomes strengthened and leaflet adaptation improved. Hence, it affects directly the underlying mitral annulus dilatation.[11,12] Small studies and meta-analysis have demonstrated both short-term and midterm reduction of MR severity, functional improvement, and reverse LV remodelling.[11,13–16] Survival has been reported up to 6 years after TMVA,[17,18] but the long-term effects on symptoms, mitral valve, and LV function are unknown. The aim of the present study was to investigate the long-term clinical and haemodynamic outcome after TMVA in a real-world patient population.

Methods

Patient population and mitral valve intervention

Consecutive patients who underwent TMVA for symptomatic secondary MR with the Carillon system between 2012 and 2018 at the University Hospital Leipzig were included in the study for prospective follow-up. The indication for TMVA was consented by the interdisciplinary heart team based on the clinical history, symptoms, co-morbidities, and mitral valve morphology and regurgitation severity at the time of index admission for symptomatic heart failure. TMVA was performed under general anaesthesia and transoesophageal echocardiographic guiding, as described recently.[11] Patients gave written informed consent. The investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee (No. 488/18-ek).

Endpoints

Clinical endpoints were all-cause mortality, heart failure hospitalizations, and additional mitral valve procedures. The main echocardiographic endpoints were MR severity (measured as regurgitant volume and regurgitant fraction), LV remodelling (i.e. LV end-systolic and end-diastolic volume index), and LV function (LV ejection fraction, forward ejection fraction, and forward cardiac index) on latest available follow-up.

Echocardiography

Baseline echocardiography was performed using Vivid E9 or E95 (GE Vingmed Ultrasound, Horten, Norway) prior to TMVA in a compensated cardiorespiratory condition, determined by the absence of signs and symptoms of congestion (i.e. pulmonary rales, orthopnoea, jugular venous dilatation, and peripheral oedema). Follow-up echocardiography was performed 45 ± 20 months (mean ± standard deviation) after TMVA. Data acquisition was carried out by an experienced echocardiographer. Analysis was conducted offline using the EchoPAC software (GE Vingmed Ultrasound). Standardized echocardiographic analysis included parasternal short-axis and long-axis views; apical long-axis (three-chamber), four-chamber, and two-chamber views; and subcostal view with M-mode, 2D, colour Doppler, Doppler, and tissue Doppler techniques according to the current recommendations.[19–21] Triplane apical views and 3D datasets were acquired if possible. LV diameters and LV mass were calculated from M-mode in the parasternal short-axis view. LV volumes, total stroke volume, and left ventricular ejection fraction (LVEF) were measured by the biplane methods of discs (modified Simpson's method) or, in case of regional wall motion abnormalities, in the triplane dataset (Supporting Information, *Figure S1* and *Data S1*). Forward stroke volume and forward cardiac output were assessed from the diameter of the LV outflow tract and pulsed-wave Doppler measurements.[22,23] Heart rate was determined simultaneously to LV outflow tract measurements. Forward ejection fraction was calculated as forward stroke volume divided by LV end-diastolic volume. Diastolic parameters were calculated from transmitral pulsed-wave Doppler and tissue Doppler at the lateral and medial mitral annulus velocity as recommended.[20] Systolic pulmonary artery pressure was estimated by maximal tricuspid valve regurgitation velocity and vena cava respiratory variability to estimate central venous pressure.[24]

Mitral regurgitation was quantified according to the recent recommendations by multi-parametric approach.[21] The ratio of the velocity time integral of the mitral valve in relation to the velocity time integral of the LV outflow tract was used as a semi-quantitative parameter.[25] Regurgitant volume was calculated as the difference of total stroke volume and forward stroke volume. Regurgitant fraction was calculated as regurgitant volume divided by total stroke volume. Effective regurgitant orifice area and regurgitant volume by the

proximal isovelocity surface area (PISA) method were measured as recommended.[21] Supporting Information, *Figure S1* (Figure legend: *Data S1*) summarizes quantitative MR assessment. Echocardiographic analysis of the acute effects of TMVA in a subset of those patients was reported recently.[13]

Statistical analysis

Categorical data were presented as absolute (%) values and continuous variables as median (with inter-quartile range). Comparisons of continuous variables between two groups were performed using the paired Wilcoxon rank-sum test or the unpaired Mann–Whitney *U* test, as appropriate. Categorical variables were compared using the χ^2 test. Survival between groups was compared with log-rank test. Hazard ratios for survival were examined using the Cox proportional regression analysis. Multivariable adjustment was performed for age, sex, and parameters with a *P* value <0.1 in the univariable analysis. Statistical analysis was performed with SPSS Version 25 (SPSS, Chicago, IL) and GraphPad Prism Version 6 (GraphPad Software, La Jolla, CA). Statistical significance was considered at a two-sided *P* value <0.05.

Results

Baseline characteristics

Thirty-three consecutive patients who underwent TMVA were included. The baseline characteristics of the patients are presented in *Table 1*. Mean age was 75 years, and 61% were women. One patient had combined primary and secondary aetiology of MR, and 32 patients suffered from secondary MR. Of those, eight were due to atrial remodelling and 24 due to LV remodelling and dysfunction. Patients were in New York Heart Association (NYHA) Functional Classes II–IV and had an elevated N-terminal pro-brain natriuretic peptide of (median) 7037 pg/mL (inter-quartile range 2341–29 152 pg/mL). The majority of patients were on guideline-directed heart failure therapy with beta-blockers, renin–angiotensin system inhibitors, and diuretics. High-risk status for mitral valve surgery was determined by a (mean) Society of Thoracic Surgeons score of 8.1% and a EuroSCORE II of 15.8%.

Table 1 Baseline clinical characteristics

Variable	Value
Number of patients	33
Age (years)	75 (54–89)
Female sex	20 (61)
Co-morbidities	
Hypertension	26 (79)
Diabetes	13 (39)
Dyslipidaemia	7 (21)
Coronary artery disease	23 (70)
Previous coronary artery bypass surgery	7 (21)
Ischaemic cardiomyopathy	14 (42)
Atrial fibrillation	25 (76)
Pacemaker and/or ICD	18 (55)
Stroke	5 (15)
Carcinoma	12 (36)
Chronic kidney disease (eGFR $<$ 60 mL/min/1.73 m^2)	22 (67)
Tricuspid regurgitation moderate or severe	19 (57)
Mitral regurgitation (MR)	
Combined primary and secondary MR	1 (3)
Secondary MR: ventricular remodelling and/or dysfunction	24 (76)
Secondary MR: atrial remodelling	8 (24)
Previous transcatheter mitral valve edge-to-edge repair	3 (9)
Biomarkers	
NT-proBNP (ng/mL)	7037 (2341–29 152)
Medications	
Beta-blockers	26 (79)
ACE inhibitors/ARB/ARNI	25 (76)
Mineralocorticoid receptor antagonists	12 (36)
Diuretics	29 (88)
Amiodarone	1 (3)
Digitalis	10 (30)
STS score (%)	8.1 ± 7.2
EuroSCORE II (%)	15.8 ± 9.8

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; eGFR, estimated glomerular filtration rate; ICD, implanted cardioverter defibrillator; NT-proBNP, N-terminal pro-brain natriuretic peptide; STS, Society of Thoracic Surgeons.
Data are presented as mean ± standard deviation, median (inter-quartile range; NT-proBNP), or numbers (%), as appropriate.

Atrial vs. ventricular mitral regurgitation

Table 2 shows the baseline echocardiographic parameters. Overall, left ventricles were dilated with increased LV mass and reduced LVEF and cardiac index. Both LA volume and systolic pulmonary artery pressure were elevated.

All patients with atrial MR exhibited atrial fibrillation. Atrial MR patients had smaller LV end-diastolic and end-systolic volumes and preserved LVEF with a similar total stroke volume index compared with patients with ventricular MR. The regurgitant volume and regurgitant fraction were comparable between groups. Effective regurgitant orifice area was smaller in atrial vs. ventricular MR. Eight patients had eccentric MR jets, similarly distributed between ventricular and atrial MR. Posterior mitral annulus calcification was present in two patients.

Clinical outcome

At follow-up after (mean ± standard deviation) 45 ± 20 months, 17 patients (52%) were dead (*Table 3* and *Figure 1A*). Of those, 13 patients had MR due to ventricular remodelling, three due to atrial remodelling and one due to combined aetiology. Mortality was similar in patients with atrial and ventricular MR (*Figure 1B*). Four patients were hospitalized for an episode of symptomatic heart failure; two of these

Table 2 Baseline echocardiographic characteristics

Variable	All patients (n = 33)	Ventricular MR (n = 24)	Atrial MR (n = 8)	P value (ventricular vs. atrial)
LV remodelling and systolic function				
LV end-diastolic septum thickness (mm)	12 (10–13)	11 (10–13)	12 (11–14)	0.314
LV end-diastolic diameter (mm)	59 (52–68)	63 (58–70)	49 (44–57)	**0.002**
LV end-systolic diameter (mm)	46 (39–56)	49 (44–60)	33 (26–39)	**0.0001**
LV end-diastolic volume index (mL/m^2)	87 (71–125)	103 (85–139)	68 (47–79)	**0.002**
LV end-systolic volume index (mL/m^2)	49 (40–81)	59 (48–95)	26 (16–38)	**<0.0001**
Total stroke volume index (mL/m^2)	38 (33–41)	38 (33–41)	39 (32–50)	0.384
LVEF (%)	38 (30–49)	35 (29–44)	64 (53–68)	**<0.0001**
Forward stroke volume index (mL/m^2)	20 (19–25)	20 (18–25)	25 (20–28)	0.126
Forward cardiac index (L/min/m^2)	1.9 (1.4–2.4)	1.8 (1.4–2.5)	2.1 (1.4–2.5)	0.641
Forward EF (%)	25 (17–32)	21 (14–28)	36 (31–48)	**0.0001**
Diastolic LV function				
E wave (m/s)	1.1 (1.0–1.2)	1.1 (0.9–1.3)	1.2 (0.9–1.4)	0.615
E' mean (m/s)	0.06 (0.05–0.07)	0.05 (0.05–0.08)	0.06 (0.06–0.08)	0.290
E/e'	18 (15–24)	19 (16–25)	17 (13–21)	0.200
Left atrial end-systolic volume index (mL/m^2)	52 (42–73)	50 (41–58)	71 (48–100)	0.056
Systolic pulmonary artery pressure (mmHg)	59 (49–70)	60 (53–71)	53 (43–77)	0.479
Mitral regurgitation quantification				
Regurgitant volume (mL)	27 (19–40)	26 (21–41)	28 (15–39)	0.875
Regurgitant fraction (%)	40 (32–49)	42 (34–51)	37 (31–44)	0.408
Effective regurgitant orifice area (cm^2) PISA	0.2 (0.2–0.35)	0.3 (0.2–0.4)	0.1 (0.1–0.2)	**0.007**
Regurgitant volume (mL) PISA	34 (30–47)	38 (31–47)	30 (26–38)	0.079

EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PISA, proximal isovelocity orifice area.
Data are presented as median (inter-quartile range). P value was calculated between atrial and ventricular MR. Statistically significant results are presented in bold.

Table 3 Clinical outcome

Events	Value
Death	17 (52%)
Patients with MR due to ventricular remodelling	13
Patients with MR due atrial remodelling	3
Patients with combined primary and secondary MR	1
Heart failure hospitalizations and additional mitral valve procedures	4
Transcatheter edge-to-edge repair	2

MR, mitral regurgitation.
Data are presented as numbers (%).

patients underwent additional transcatheter mitral valve intervention with edge-to-edge repair due to recurrent MR (*Table 3*).

Predictors for mortality by univariable and multivariable Cox regression analysis are shown in *Table 4*. While there was an association of baseline total stoke volume and LA end-systolic volume with mortality in univariable analysis, no significant association was found after multivariable adjustment.

Echocardiographic haemodynamics at follow-up

Ten patients were available for echocardiographic follow-up. Blood pressure was similar at baseline and at follow-up. Both NYHA functional class and MR severity were improved at follow-up (*Figure 2*). Regurgitant volume and regurgitant fraction were reduced (*Table 5*). This was associated with decreased end-diastolic and end-systolic LV diameters and volumes (*Table 5*). Both LVEF (43% vs. 54%, P = 0.014) and forward ejection fraction (23% vs. 45%, P = 0.006) were increased, while forward cardiac index was similar to baseline. However, forward stroke volume index tended to increase (20 vs. 26 mL/m^2, P = 0.084), while heart rate was numerically lower (84 vs. 69 b.p.m., P = 0.264).

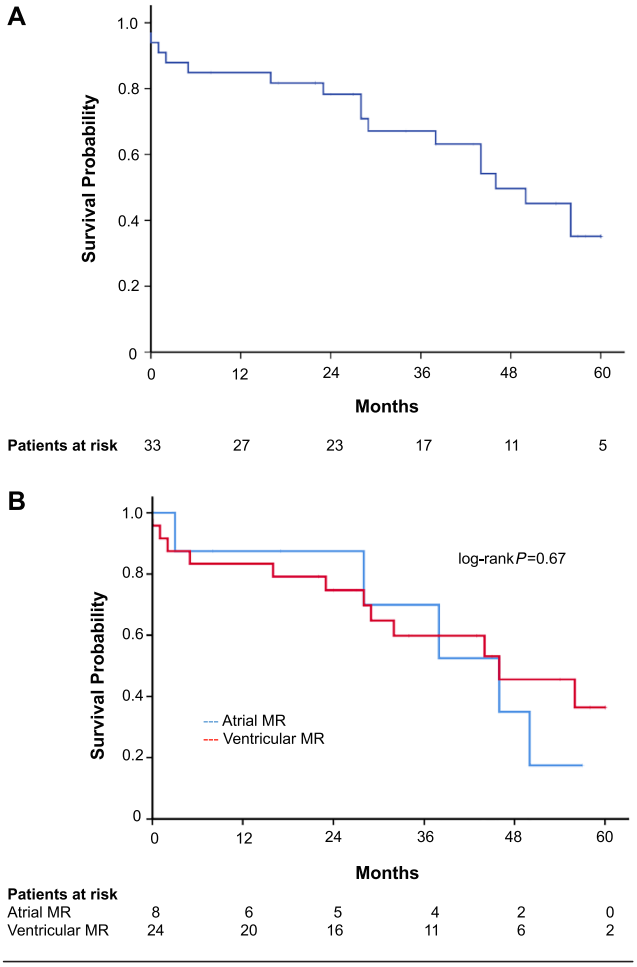
Reductions of regurgitant fraction and LV volumes as well as increases in LVEF were similar in patients who experienced heart failure hospitalization (n = 4) during follow-up and those who did not (n = 6). At baseline, LV volumes, LV function, and MR severity were similar among these patient groups (data not shown).

The doses of beta-blockers were similar at baseline and at follow-up, while those of inhibitors of the renin–angiotensin system (i.e. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor neprilysin inhibitors) were increased at follow-up (P = 0.004) (Supporting Information, *Figure S2* and *Data S1*). After TMVA, there were no coronary (percutaneous or bypass surgery) or aortic valve interventions during the study period.

Discussion

This observational study is the first report of long-term clinical and haemodynamic results after TMVA. The data demonstrate that among high-risk patients undergoing TMVA

Figure 1 Kaplan–Meier analysis of survival. (A) Probability of survival during the follow-up period of patients treated with transcatheter mitral annuloplasty for symptomatic secondary mitral regurgitation (MR). (B) Probability of survival of ventricular and atrial MR. One patient with combined primary and secondary MR was excluded from this analysis.



for symptomatic secondary MR, mortality is ~50% at 4 years. In the limited number of patients available for follow-up echocardiography, reduction of MR was associated with reduced NYHA functional class, reverse LV remodelling, and improved LV function (*Figure 3*).

Ventricular vs. atrial mitral regurgitation

An important mechanism of secondary MR is mitral annulus dilatation, due to either ventricular or atrial dilatation.[2,8] The subgroup analysis of ventricular vs. atrial remodelling showed that patients with ventricular MR exhibit typical features of heart failure with reduced ejection fraction, that is, LV dilatation and LV systolic dysfunction. In contrast, patients with atrial MR had concentric LV remodelling and preserved LV systolic function, while both absolute forward cardiac output and MR quantification were similar to patients with ventricular remodelling. LA volume tended to be larger in atrial MR, presumably due to atrial fibrillation, which was present in all patients. Because LV diastolic dysfunction and signs of elevated LV filling pressures were similar in both groups, patients with atrial remodelling resemble some characteristics of patients with heart failure with preserved ejection fraction.[26]

Transcatheter approaches to treat secondary mitral regurgitation

From a pathophysiological point of view, a treatment approach directed to the predominant mechanism of secondary MR seems to be preferable, by either a surgical or interventional approach.[2] The most widely used transcatheter edge-to-edge repair technique can be used to treat both primary and secondary MR.[27–29] However, mitral leaflets are structurally affected by the clip, and increased post-procedural mitral valve gradients may occur and negatively impact the clinical benefit of this therapy.[30,31] We recently demonstrated both short-term and long-term improved haemodynamics in patients undergoing transcatheter edge-to-edge repair.[28,29] Two large, randomized clinical trials in secondary MR yielded conflicting clinical results of transcatheter edge-to-edge repair.[32,33] Therefore, there is a need for further clinical studies to evaluate the effects of any mitral valve intervention in secondary MR.

Long-term clinical outcome after transcatheter mitral valve annuloplasty

The randomized, sham-controlled REDUCED-FMR trial in patients with secondary MR demonstrated reduced regurgitant volume at 12 months after TMVA (the primary endpoint) as well as reverse LV remodelling.[14] These data are similar to that of the previous TITAN trial, which showed improved functional status up to 24 months after TMVA.[15] An individual meta-analysis of TMVR studies confirmed symptomatic and echocardiographic improvement at 12 months.[16] Long-term follow-up of these patients revealed survival rates of 50–60% 5 years after TMVR.[17,18] In our study, mortality steadily increases up to ~50% after 4 years. This slightly higher mortality may be attributed to an advanced stage of heart failure stage with high N-terminal pro-brain natriuretic peptide levels, 95% of patients in NYHA Classes III and IV, and low forward cardiac index, that is, a high-risk population.[34]

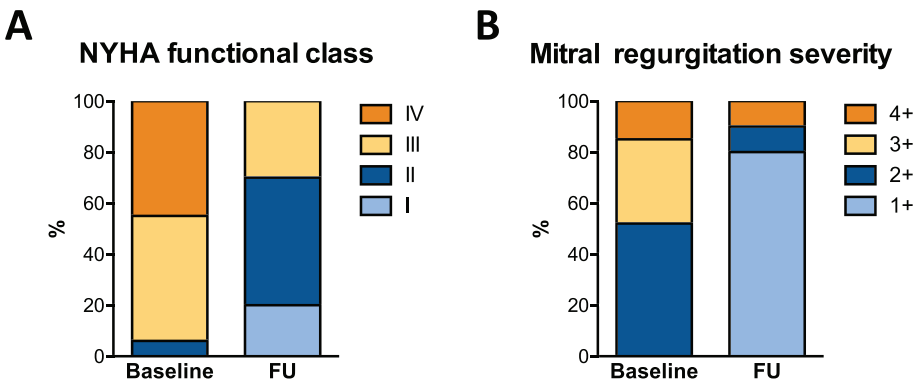
Prognostic data about atrial MR are scarce.[26] Our results suggest that prognosis of patients with atrial MR is similar to those with ventricular MR, thus requiring efforts to optimize treatment and prognosis. These data reflect the high burden of morbidity and mortality of patients with secondary

Table 4 Predictors for mortality

	Univariable		Multivariable	
Parameter	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	0.996 (0.95–1.04)	0.871		
Gender	0.645 (0.25–1.68)	0.368		
eGFR	0.998 (0.98–1.02)	0.825		
Troponin T	0.964 (0.89–1.05)	0.408		
Heart rate	0.967 (0.93–1.004)	0.083	1.003 (0.94–1.02)	0.262
LVEF (%)	1.004 (0.97–1.04)	0.801		
LV end-diastolic volume	1.010 (0.99–1.03)	0.239		
LV end-systolic volume	0.989 (0.97–1.01)	0.318		
Total stroke volume	**1.068 (1.02–1.12)**	**0.004**	1.063 (0.99–1.13)	0.054
Forward stroke volume	1.007 (0.98–1.04)	0.656		
Forward cardiac index	0.589 (0.22–1.57)	0.290		
Forward EF	0.980 (0.93–1.03)	0.411		
Left atrial end-systolic volume	**1.006 (0.99–1.01)**	**0.050**	1.003 (0.99–1.01)	0.496
E wave	2.244 (0.23–21.61)	0.484		
E/e'	0.934 (0.85–1.02)	0.135		
Systolic pulmonary artery pressure	1.000 (0.97–1.03)	0.982		
Regurgitant volume	1.019 (0.99–1.05)	0.215		
Regurgitant fraction	1.037 (0.99–1.09)	0.130		

CI, confidence interval; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction.
Multivariate adjustment was performed for age, sex, heart rate, left atrial end-systolic volume, and total stroke volume. Statistically significant results are presented in bold.

Figure 2 Symptom status and mitral regurgitation severity at baseline and at follow-up (FU). (A) New York Heart Association (NYHA) functional class and (B) mitral regurgitation severity at baseline and at FU.



MR for whom the transcatheter approach might reduce symptoms due to MR.

Assessment of mitral regurgitation

Mitral regurgitant volume and regurgitant fraction are suitable to quantify MR severity during mitral valve interventions, as demonstrated by others and our previous study.[13,35] In contrast, the PISA method requires a well-defined proximal convergence zone, which can be small or undetectable in mild or even unreliable in eccentric jets, which occurs also in atrial MR.[36] Because eccentric MR jets were distributed similarly in atrial and ventricular MR, the PISA method might underestimate MR severity in atrial MR because regurgitant volume and regurgitant fraction were similar between these entities. Thus, a quantitative approach seems preferable for grading MR severity and to monitor MR in patients undergoing mitral valve interventions. Our study provides important clinical and haemodynamic outcome in well-characterized patients with secondary MR.

Left ventricular remodelling and left ventricular function

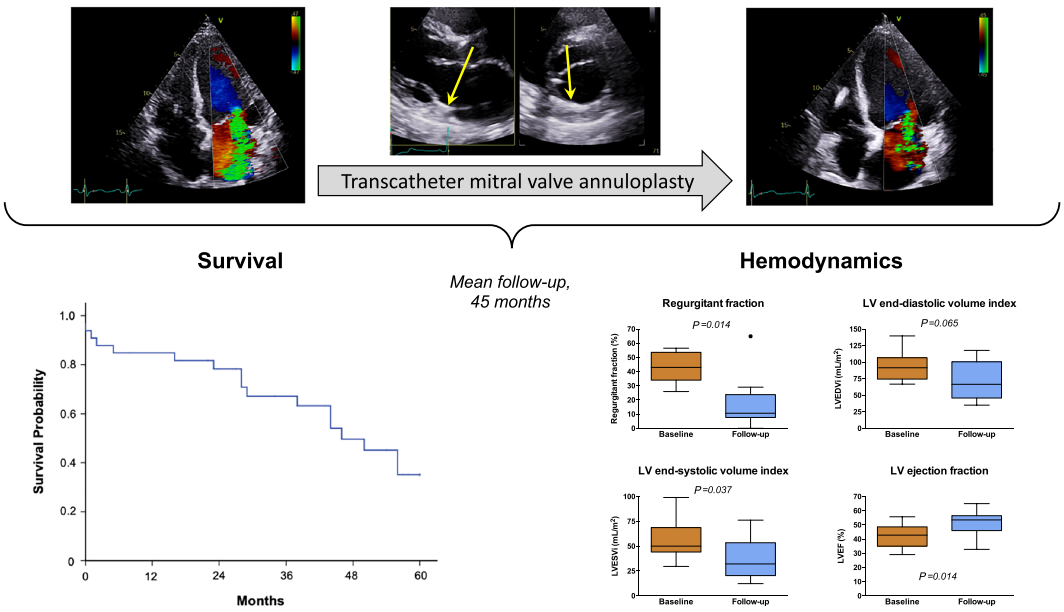
Haemodynamic outcome beyond 12 months after TMVA is currently unknown. Our study shows that sustained reduction of MR at follow-up in the surviving patients was associated with reverse LV remodelling, that is, reduced LV

Table 5 Echocardiographic parameters at baseline and follow-up

Variable	Baseline (n = 10)	Follow-up (n = 10)	Difference (median)	P value
Vital parameter				
Heart rate (b.p.m.)	84 (68–93)	69 (64–76)	−4.5	0.264
Systolic blood pressure (mmHg)	158 (122–165)	137 (121–161)	−9.0	0.477
Diastolic blood pressure (mmHg)	80 (70–90)	78 (66–96)	−0.5	0.922
LV remodelling and systolic function				
LV end-diastolic septum thickness (mm)	12 (10–14)	12 (10–13)	0	0.563
LV end-diastolic diameter (mm)	60 (55–64)	55 (50–61)	−0.3	**0.012**
LV end-systolic diameter (mm)	46 (39–57)	40 (33–46)	−0.4	**0.048**
LV end-diastolic volume index (mL/m^2)	92 (74–107)	67 (46–101)	−21.6	0.065
LV end-systolic volume index (mL/m^2)	50 (44–69)	32 (20–53)	−15.2	**0.037**
Total stroke volume index (mL/m^2)	38 (33–43)	33 (26–44)	−3.6	0.695
LVEF (%)	43 (35–49)	54 (46–57)	4.9	**0.014**
Forward stroke volume index (mL/m^2)	20 (19–26)	26 (21–35)	3.5	0.084
Forward cardiac index (L/min/m^2)	1.7 (1.3–2.5)	1.9 (1.6–2.8)	0.4	0.375
Forward EF (%)	23 (19–31)	45 (30–54)	17.5	**0.006**
Diastolic LV function				
E wave (m/s)	1.1 (0.9–1.3)	1.0 (0.9–1.4)	−0.1	0.748
E′ mean (m/s)	0.07 (0.05–0.09)	0.07 (0.07–0.08)	0	0.406
E/e′	17.8	14.4	−2.5	0.232
Left atrial end-systolic volume index (mL/m^2)	47 (41–56)	60 (39–69)	5.9	0.275
Systolic pulmonary artery pressure (mmHg)	67 (39–80)	49 (42–80)	3.5	0.641
Mitral valve function				
Regurgitation volume (mL)	27 (25–42)	8 (3–17)	−22.0	**0.018**
Regurgitation fraction (%)	42 (34–54)	11 (8–24)	−33.9	**0.014**
Effective regurgitation orifice area (cm^2) PISA	0.25 (0.18–0.33)	0.15 (0.10–0.28)	−0.05	0.375
Regurgitation volume (mL) PISA	42 (31–48)	26 (15–44)	−20.5	0.156
MV mean diastolic gradient	2.4 (1.7–3.1)	1.6 (1.1–4.0)	−0.9	0.688

EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MV, mitral valve; PISA, proximal isovelocity orifice area.
Data are presented as absolute values (%) or median (inter-quartile range), as appropriate. Statistically significant results are presented in bold.

Figure 3 Long-term clinical and haemodynamic outcome in patients with secondary mitral regurgitation treated with transcatheter mitral valve annuloplasty. Transcatheter mitral valve annuloplasty with Carillon device implantation in the coronary sinus (echo rich on biplane transthoracic parasternal views, yellow arrows) reduced mitral regurgitation severity. After a mean follow-up of 45 months, mortality was 52%. In the remaining patients—including two patients undergoing additional edge-to-edge mitral valve repair—reduced regurgitation fraction in the long-term was associated with reduced left ventricular (LV) end-diastolic volume index (LVEDVi) and LV end-systolic volume index (LVESVi) and increased LV ejection fraction (LVEF), that is, reverse LV remodelling and improved LV function.



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volumes and diameters and improved LV function. Both LVEF and forward ejection fraction, which is a more accurate parameter of LV function than LVEF in MR,[28,37] were increased after TMVA. While forward cardiac index remained similar at follow-up, forward stroke volume numerically increased while heart rate decreased (without statistical significance, probably due to the small number of patients). These changes can be interpreted as sign of a haemodynamic improvement.

In case of persistent or recurrent MR after TMVA, the transcatheter edge-to-edge repair offers an additional approach to obtain an optimal result of long-term MR reduction. The transcatheter treatment resulted reduced MR severity and improved LV parameters at follow-up in all but one patient. This observation was consistent in patients with and without event during follow-up.

In summary, these data demonstrate a favourable long-term effect of TMVA on MR severity, which is associated with reverse LV remodelling and improved LV function (*Figure 3*).

Limitations

This is an observational study of patients who underwent TMVA. The lack of a control group is a limitation for the interpretation of the clinical and echocardiographic outcome measures. This applies particularly for NYHA functional class, which is prone to bias. Unfortunately, the causes of mortality are not available from our study. The number of patients available for follow-up was small, primarily because of high mortality, and represents a selected population due to survival bias. The small sample size of the study is a limitation for Cox regression and subgroup analysis, which should be interpreted as hypothesis generating. However, the data may provide important insights into this area with very limited published data available. Optimal medical treatment is the mainstay of therapy for chronic heart failure.[6] Increased doses of renin–angiotensin system inhibitors at follow-up may have contributed to reduced MR severity and improved LV function.[6,38,39]

Conclusions

This report on long-term results of patients treated with transcatheter annuloplasty for secondary MR showed a significant mortality (~50%) at 4 years. Despite the limited number of patients available for follow-up, reduction of MR was associated with reverse LV remodelling and improved cardiac haemodynamics. The study provides important long-term data from a real-world population, which may help to design randomized controlled trials powered for clinical endpoints.

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Conflict of interest

D.L. received speaker honoraria from Cardiac Dimensions. J. B., T.S., S.S., and U.L. declared no conflicts of interest. A.H. received speaker honoraria from Cardiac Dimensions.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1: Quantitative assessment of mitral regurgitation.
Figure S2: Heart failure medication at baseline and at follow-up
Data S1. Supporting information

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